Reply to 'Different outcome variables yield different results', by O. Brouckaert et al.

We thank Brouckaert et al. [1] for their comments on our paper, in which they question our finding of a lack of effect of chemotherapy in postmenopausal patients with invasive lobular breast cancer (ILC).

The study by von Minckwitz et al. indeed seems to indicate that pathologic complete remission may not be a good predictor for the ultimate prognosis in patients with ILC [2]. But the fact remains that also in this study the likelihood of a pathologic complete response was rare (<10%) in patients with ILC and more than twofold lower than in those with invasive ductal cancer (IDC). And so far, we are still looking for the biological mechanisms which could explain this lack of response to neoadjuvant chemotherapy in patients with ILC.

For any factor to be a true confounder, it needs to be associated with the likelihood of receiving chemotherapy as well as with the overall survival. Unlike histological grade, for which we have adjusted in the multivariable analysis, vascular invasion and HER2 status have never been mentioned as criteria for the use of chemotherapy in the Dutch treatment guidelines, neither in patients with ILC nor in those with IDC. The same holds true for comorbidity, frailty or other factors that might limit general life expectancy. Although they may have influenced the decision to use chemotherapy in the patients observed in our study, it is very unlikely that that this influence was dependent on the histological type of the study and could thus explain the differences observed between ILC and IDC with respect to the effect of chemotherapy.

We have tried to rule out the impact of the estrogen (ER) and progesterone receptor (PR) status on our findings by restricting our study population to patients who received hormonal treatment, assuming that they all had a positive ER and/or PR status. We agree with Brouckaert and colleagues that it would be interesting to see if and to what extent the levels of ER and PR expression are responsible for the differences in sensitivity to chemotherapy between ILC and IDC. Currently, we are planning such a study. A recent study of patients enrolled in the Tamoxifen Exemestane Adjuvant Multinational trial did not show any significant differences between ILC and IDC when looking at semi-quantitative ER expression levels according to the Allred score, but this score may not be sensitive enough [3].

As we have also clearly stated in the discussion of our paper, we are well aware of the limitations of the observational design of our study and thus, do not dispute the view that our results need to be validated by other studies before they can lead to a change in the treatment of patients with ILC. We hope that our findings and the clinical importance of the question are convincing enough to stimulate others to provide evidence from randomized data.

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disclosure

The authors have declared no conflicts of interest.

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Staging for distant metastases in operable breast cancer: a suggested expansion of the ESMO guideline recommendation for staging imaging of node-negative, hormonal receptor-negative disease

We evaluated the impact of staging procedures to detect asymptomatic distant metastases (DM) in the management of women with operable invasive breast cancer (BC, entire cohort: $n = 866$). Out of 472 patients with lymph node (LN)-negative disease (pN0), DM were found in four cases (detection rate: 0.8%). All four patients presented with established risk factors: hormone receptor (HR)-negative status, HER2-positive status, $n = 3$; 'triple-negative' disease, $n = 1$. Considering the subgroup of LN-negative patients whose tumors showed the risk factor 'negative HR status' ($n = 66$), the detection rate of DM was 6%. The detection rates of DM in higher pN categories were as follows: pN1:1.7%; pN2:9.5%; pN3:13.5%. We generally support the international guidelines, including those published by the European Society for Medical Oncology (ESMO) which emphasize that patients with early-stage BC do not profit from radiological staging for the detection of DM and recommend refraining from this. However, we would expand these guidelines and propose that screening should be carried out in node-negative patients whose tumors show established tumor-related risk factors (e.g. HR-negative and HER2-positive status), since in this particular subcohort, the detection rate of DM is with 6% similarly high as that of patients with four to nine positive LNs.

The incidence of detectable metastatic disease at the time of breast cancer (BC) diagnosis is extremely small in patients with early-stage lymph node (LN)-negative disease. Regarding the question whether diagnostic procedures for the detection of

potential distant metastases (DM) are appropriate and efficient, the literature defined a 1% cut-off for clinical usefulness [1]. According to this, the current international guidelines for the management of women with operable BC generally recommend against routine use of staging imaging studies to detect asymptomatic DM in patients who have axillary LN-negative disease [2, 3].

Since in Switzerland many breast centers still carry out general radiological screening for DM in all patients with operable BC, we evaluated the impact of this procedure using Swiss data. We analyzed data from the University Women's Hospital Basel (Basel, Switzerland) from a time period in which such a general screening (chest X-ray, abdominal ultrasound and bone scintigraphy) was still being routinely conducted at our institution.

All invasive BC patients who underwent primary surgery with axillary staging between 1990 and 2004 at our institution and had no clinical symptoms indicating the presence of DM form the basis of this study ($n = 866$, Table 1, Part A). Out of 472 patients with LN-negative disease (pN0), DM were found in four cases (detection rate: 0.8%). All four patients presented with established risk factors: hormone receptor (HR)-negative status, HER2-positive status, $n = 3$; 'triple-negative' disease, $n = 1$; Table 1, Part B. Considering the subgroup of LN-negative patients whose tumors showed the risk factor 'negative HR status' ($n = 66$), the detection rate of DM was 6%. In patients who had one to three positive LNs (pN1, $n = 237$), four women were found to have DM (detection rate: 1.7%). None of these cases had either of the risk factors 'HR negative' or 'HER2 positive'. The detection rates of DM in higher pN categories were as follows: pN2 (4–9 positive LNs): 9.5% (8 of 84 patients); pN3 (≥10 positive LNs): 13.5% (10 of 74 patients).

conclusion

We generally support the international guidelines, including those published by the European Society for Medical Oncology (ESMO) which emphasize that patients with early-stage BC do not profit from radiological staging for the detection of metastatic disease and recommend refraining from this [2]. However, we would expand these guidelines and propose that screening should be carried out in the subgroup of node-negative patients whose tumors show established tumor-related risk factors (e.g. HR-negative and HER2-positive status), since in this particular subcohort, the detection rate of DM is not

Table 1. Part A: Clinicopathological features in 866 cases with operable breast cancer (1990–2004). Part B: Four patients who had node-negative disease but had distant metastases (DM) diagnosed at the time of initial diagnosis.

	Entire cohort $n = 866$	pN0 $n = 472$ (54.5%)	pN1 $n = 237$ (27.4%)	pN2 $n = 84$ (9.7%)	pN3 $n = 73$ (8.4%)
Part A					
Cases with DM (%)	26 (3.0)	4 (0.8)	4 (1.7)	8 (9.5)	10 (13.5)
Median age (range)	60 (26–90)	60 (26–88)	60 (28–88)	56 (32–89)	60 (30–90)
Median tumor size (mm) (range)	20 (<1–140)	16 (<1–84)	22 (5–70)	25 (6–100)	35 (11–140)
Median number of axillary LNs removed (range)[a]	17 (1–54)	16 (1–54)	17 (2–46)	19 (7–38)	23 (11–51)
Hormone receptor (HR) status					
Known	834	447	231	83	73
positive (%)	694 (83.2)	385 (86.1)	196 (84.8)	63 (75.9)	50 (68.5)
Grading					
Known	819	442	224	81	72
G3 (%)	394 (48.1)	183 (41.4)	114 (50.9)	47 (58.0)	50 (69.4)
HER2 status					
Known	524	278	138	60	48
positive (%)	105 (20.0)	50 (18.0)	23 (16.7)	16 (26.7)	16 (33.3)
Part B	Case 1	Case 2	Case 3	Case 4	
Year of intial diagnosis	1995	2000	2000	2004	
Patient's age at initial diagnosis	54	70	78	63	
Tumor size (mm)	24	18	21	30	
Number of axillary LNs removed	23	7	13	1 (sentinel LN)	
Site of DM	HEP	OSS	LYM	OSS	
Grading	2	3	3	3	
HR status	Negative	Negative	Negative	Negative	
HER2 status	Positive	Positive	Negative	Positive	
Outcome: died of metastatic BC	Yes	Yes	Yes	Yes	
Survival time (months)	16	4	20	34	

[a]In 2003 a sentinel LN biopsy was established as a standard procedure.

LN: Lymph nodes; BC: breast cancer; Site of DM: HEP = hepatic; OSS = osseous; LYM = lymph nodes, excluding axilla (in the particular case reported: supraclavicular, cervical and mediastinal LN).

negligible. In fact, the 6% detection rate in these patients is similar to that of patients with four to nine positive LNs. According to current therapy guidelines, patients who have HR-negative BC usually receive adjuvant multidrug chemotherapy. It is exactly these patients who should have additional diagnostic procedures carried out in order to exclude DM and thereby confirm the adjuvant situation, which justifies aggressive combination chemotherapy.

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disclosure

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Reply to 'Staging for distant metastases in operable breast cancer: a suggested expansion of the ESMO guideline recommendation for staging imaging of node-negative, hormonal receptor-negative disease' by U. Gueth et al

Dr Güth et al. [1] report an analysis of postoperative staging of patients with breast cancer in the University of Basel cohort. Their main message is that their patients with ER-negative apparent stage I breast cancer have a similar probability of distant metastases as patients with apparent stage II disease. Based on their data, it would seem logical to apply the same protocols of staging to patients with 'high-risk stage I' breast cancer.

The rationale of adjuvant therapy is the eradication of distant metastases at a time when they are not detectable by clinical methods. In the last decade, adjuvant therapy has become more effective with the introduction of taxanes, trastuzumab, and aromatase inhibitors; this implies that a higher number of micrometastases can be eliminated by therapy. Thus, the traditional concept of 'cM0' in TNM terminology is open to question, and the naïve use of sophisticated staging methods changes or undermines the meaning of the term 'adjuvant'. The threshold probability of distant metastases above which staging procedures are considered useful depends not only on the cost and convenience of screening, but also on the efficacy of current therapeutic options. The conventional staging procedures such as bone scans, chest radiographs, and abdominal ultrasound examinations have been used in most clinical trials of adjuvant therapy. They traditionally directed therapy by identifying patients with advanced disease who were not amenable to medical cure. This is not the case for other staging methods such as the detection of epithelial cells in bone marrow aspirates. In the context of current adjuvant therapies, it is conceivable that overdiagnosis of distant disease by more sensitive staging techniques including computed tomography with positron emission tomography may not prevent overtreatment of incurable disease but lead to undertreatment of potentially curable patients.

The performance of most staging methods has been evaluated only in terms of diagnostic accuracy but not in terms of patient outcome. At present, the relative merits of different staging methods are subject to numerous biases as is reflected in the range of recommendations in different clinical guidelines. Clinical trials investigating the value of different staging algorithms are needed to avoid over- and undertreatment. In this context, Dr Güth's comments are well taken and will be considered in the development of a future update of the guidelines.

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